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**Citation:** Eavarone, David A., Venkataramanan Soundararajan, Toomas Haller, and Ram Sasisekharan. "A Voxel-Based Monte Carlo Model of Drug Release from Bulk Eroding Nanoparticles." *Journal of Nanoscience and Nanotechnology* 10, no. 9 (September 1, 2010): 5903–5907.

**As Published:** <http://dx.doi.org/10.1166/jnn.2010.2456>

**Publisher:** American Scientific Publishers

**Persistent URL:** <http://hdl.handle.net/1721.1/89031>

**Version:** Author's final manuscript: final author's manuscript post peer review, without publisher's formatting or copy editing

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Published in final edited form as:

*J Nanosci Nanotechnol*. 2010 September ; 10(9): 5903–5907.

## A Voxel-Based Monte Carlo Model of Drug Release from Bulk Eroding Nanoparticles

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### Abstract

The use of polymeric nanoparticles as drug delivery devices is becoming increasingly prevalent in a variety of therapeutic applications. Despite their widespread clinical use, the factors influencing the release profiles of nanoparticle-encapsulated drugs are still not quantitatively understood. We present here a new, semi-empirical model of drug release from polymeric nanoparticles using a formulation of dexamethasone encapsulated within poly(lactic-co-glycolic acid) to set model parameters. We introduce a three-dimensional voxel-based framework for Monte Carlo simulations that enables direct investigation of the entire spherical nanoparticle during particle degradation and drug release. Due to implementation of this model at the nanoscale, we utilize assumptions that simplify the model while still allowing multi-phase drug release to be simulated with good correlation to experimental results. In the future, emerging mechanistic understandings of nanoparticle drug release may be integrated into this simulation framework to increase predictive power.

### Keywords

Nanoparticles; Monte Carlo Model; Drug Release

The shift from micro- to nano- scale drug delivery systems in recent decades has been driven by improvements in polymer formulation technology and evidence that medical applications such as chemotherapy are significantly enhanced by the use of nanoscale delivery vehicles.<sup>1–4</sup> Because drug release profiles differ based on the polymer, drug, and design parameters, the availability of computational models to understand and predict drug release is valuable for the extension and optimization of existing drug delivery technologies.

Several models have been reported in the literature to describe drug release and particle breakdown for polymer-based delivery vehicles.<sup>5–8</sup> It is clear from these studies that the number of factors influencing drug release is too unwieldy for a single model to incorporate. Such factors include water and drug diffusion, drug dissolution, polymer molecular weight, particle size and geometry, polymer degradation, micro-environment pH changes, autocatalysis, polymer swelling, and more.<sup>9–11</sup> Incorporation of these factors is further complicated by a still incomplete understanding of the extent to which they each influence the kinetics of drug release. Previous modeling approaches have been limited by necessity to incorporating the factors most influential to drug release or polymer breakdown for a particular delivery system.<sup>10</sup> Despite this limitation, computational models have still successfully simulated complex multi-phase drug release profiles from polymeric microparticles.<sup>12–15</sup> Few studies have extended these models to polymeric nanoparticles, though these are becoming prominent in therapeutic applications.<sup>16</sup>

The mechanism of drug release from nanoparticles may differ from that of microparticles even when both vehicles have the same polymer composition. Drug diffusion through the polymer matrix has been shown to be slower in nanoparticles than in microparticles, and this may be due to more dense internal structures as a result of fabrication techniques or the neutralization of autocatalysis-enhanced diffusion phenomenon at the smaller length scales.<sup>8,9,17</sup> For the purposes of our model, we postulate that the reduced drug diffusivity in nanoparticles limits the influence of diffusion in the model to the interface between polymer and the external aqueous environment. That is, we assume that drug release occurs only after degradation of surrounding polymer and the formation of an erosion channel to the particle surface. Once the drug diffuses into the exposed erosion channel, the drug is considered to be released due to the small distances necessary to travel to the particle surface at the nanoscale. Using this framework, we model drug release from bulk eroding nanoparticles based upon a three dimensional Monte Carlo simulation of polymer erosion.

For the Monte Carlo simulation presented here, entire spherical nanoparticles are represented using voxels. A voxel is the volume element which represents data on a regular grid in three dimensional space and is analogous to a pixel which is the area element representing data in two dimensions.<sup>18</sup> Previous two dimensional models have depicted drug release from a pixel as dependent upon the state of the pixel's immediate 8 neighbors.<sup>12,14</sup> In this three dimensional voxel-based model, we assess the influence of the 18 neighbors most immediately surrounding the voxel in order to give the best representation of a sphere (Fig. 1). The State Diagram (Fig. 2) describes the simulation algorithm governing voxel dynamic state transitions ( $x_{i,j,k}$ ) and voxel drug release. Assuming a homogeneous mixture of drug and polymer, each voxel begins with a voxel dynamic state ( $x_{i,j,k}$ ) of 1. The lifetime of individual voxels follows a Poisson's distribution given by:

$$T_{i,j,k}^L(t) = -\ln(\varepsilon/\lambda) \quad (1)$$

where  $\varepsilon$  is a random number and  $1/\lambda$  is the half life of the polymer system. Expiration of this lifetime changes the voxel dynamic state ( $x_{i,j,k}$ ) to zero and the polymer is considered degraded. In order for the polymer to be considered eroded, access to the aqueous environment via an erosion channel from the surface of the nanoparticle is required. Such a

channel is formed when at least one of the 18 immediate neighboring voxels is eroded, i.e., any of the neighbor's dynamic voxel state ( $x_{i,j,k}$ ) becomes  $-1$ .

We formulated poly(lactic-co-glycolic acid) (PLGA) nanoparticles encapsulating the hydrophobic agent dexamethasone as described in Figure 3. Hydrolysable polymers such as PLGA are often used in the formulation of nanoparticles as they combine sustained drug release with complete biodegradability.<sup>21</sup> The polymer half life ( $1/\lambda$ ) is approximated at 0.121 days from previous measurements in the literature.<sup>22</sup> In order to run the model simulation, we used the drug release data from this formulation to fit values for two parameters: the number of voxels ( $N$ ) that compose each nanoparticle and a parameter ( $\kappa$ ) that integrates the influence of mass transport phenomenon into the simulation. The parameter  $\kappa$  (value between 0 and 1) measures the likelihood of drug release from an intact voxel into an aqueous erosion channel upon exposure, and represents the combined contributions of drug diffusion and dissolution on drug release at this interface. The parameter  $N$  is related to the physical size of the particle and also controls the surface area to volume ratio. Polymeric nanoparticles have a higher surface area to volume ratio than microparticles which may lead to a more pronounced relative initial burst of drug release.

The experimental release profile of dexamethasone from PLGA nanoparticles shows an initial burst release of 40% over the first ~25 hours. A more sustained phase of drug release occurs over the next ~120 hours resulting in complete release of encapsulated drug by 150 hours. The model simulation was a good match to experimental drug release with a coefficient of determination ( $R^2$ ) value of 0.96 (Fig. 3). We are also able to use our model simulation to investigate physical properties of the voxelated nanosphere during erosion by exploring the fragment size distribution and average size of the nanoparticles over time (Fig. 4(a)). Percolation-driven particle breakdown due to bulk erosion is shown to occur after 150 hours, and so does not appear to play a dominant role in drug release. A plot of nanoparticle surface area/volume with respect to time (Fig. 4(b)) indicates an initial lag prior to the formation of erosion channels. This corresponds well with the lag before the change in phase of experimental drug release from initial burst to sustained release (Fig. 3).

The potential of extending this model to additional drug formulations is explored through variation in the parameter  $\kappa$  (Fig. 5). The influence of  $\kappa$  is restricted to drug release at the interface of polymer and the external aqueous environment. A  $\kappa$  value of 1 corresponds to immediate drug release from an exposed intact voxel into an erosion channel, and the resultant rapid drug release profile is consistent with that of a highly hydrophilic drug.<sup>23</sup> A  $\kappa$  value of 0 indicates that drug release from an exposed intact voxel does not occur until the voxel is degraded, and the resultant sustained drug release profile is consistent with that of a polymer-conjugated drug.<sup>24</sup> Values of  $\kappa$  between 0 and 1 correspond with intermediate capacities for drug release from an exposed intact voxel, and the resultant multi-phase drug release profiles are consistent with that of a hydrophobic drug as presented here.

Because all processes that influence drug release are not yet quantitatively understood, there is value to the use of semi-empirical computational models able to simulate multi-phase drug release profiles. Use of the model presented here does not require knowledge of physical parameters such as polymer porosity, drug solubility, and drug diffusivity which

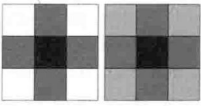
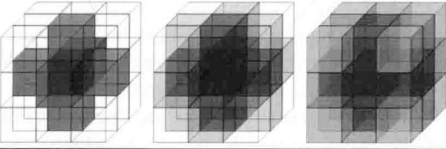
are often not available or can be difficult to measure. Voxellation of the entire nanoparticle facilitates the extension of this platform to non-symmetrical vehicle formulations as well as non-uniform drug and polymer distributions. Variation of the parameter  $\kappa$  demonstrates the versatility of this model for simulating release of hydrophilic, hydrophobic, and polymer-conjugated drugs. This model was intended as a proof of principle, however in the future emerging mechanistic understandings of phenomenon influencing nanoparticle drug release may be incorporated to further increase accuracy and strengthen predictive power.

## Acknowledgments

The authors thank G. Franzesi and P. Shum for assistance with release experiments, and Dr. A. Chandrasekaran and A. Ziolkowski for helpful comments on the manuscript. The work was supported by NIH GM57073.

## References and Notes

1. LaVan DA, McGuire T, Langer R. *Nat Biotech.* 2003; 21:1184.
2. Sengupta S, Eavarone D, Capila I, Zhao G, Watson N, Kiziltepe T, Sasisekharan R. *Nature.* 2005; 436:568. [PubMed: 16049491]
3. Gref R, Minamitake Y, Peracchia MT, Trubetskoy V, Torchilin V, Langer R. *Science.* 1994; 263:1600. [PubMed: 8128245]
4. Panyam J, Labhasetwar V. *Adv Drug Deliv Rev.* 2003; 55:329. [PubMed: 12628320]
5. Gopferich A. *Biomaterials.* 1997; 18:397. [PubMed: 9061180]
6. Zygorakis K, Markenscoff PA. *Biomaterials.* 1996; 17:125. [PubMed: 8624389]
7. Gopferich A, Langer R. *AIChE Journal.* 1995; 41:2292.
8. Polakovic M, Gorner T, Gref R, Dellacherie E. *J Controlled Release.* 1999; 60:169.
9. Arifin DY, Lee LY, Wang CH. *Adv Drug Deliv Rev.* 2006; 58:1274. [PubMed: 17097189]
10. Siepmann J, Gopferich A. *Adv Drug Deliv Rev.* 2001; 48:229. [PubMed: 11369084]
11. Gopferich A. *Biomaterials.* 1996; 17:103. [PubMed: 8624387]
12. Gopferich A, Langer R. *Macromolecules.* 1993; 26:4105.
13. Faisant N, Siepmann J, Benoit JP. *Eur J Pharm Sci.* 2002; 15:355. [PubMed: 11988397]
14. Siepmann J, Faisant N, Benoit JP. *Pharm Res.* 2002; 19:1885. [PubMed: 12523670]
15. Zhang M, Yang Z, Chow LL, Wang CH. *J Pharm Sci.* 2003; 92:2040. [PubMed: 14502543]
16. de la Zerda A, Gambhir SS. *Nat Nano.* 2007; 2:745.
17. Liggins RT, Burt HM. *Int J Pharm.* 2001; 222:19. [PubMed: 11404029]
18. Arie EK. *ACM Comput Surv.* 1996; 28:165.
19. Cascone MG, Pot PM, Lazzeri L, Zhu Z. *J Mater Sci Mater Med.* 2002; 13:265. [PubMed: 15348623]
20. Panyam J, Williams D, Dash A, Leslie-Pelecky D, Labhasetwar V. *J Pharm Sci.* 2004; 93:1804. [PubMed: 15176068]
21. Siepmann J, Elkharraz K, Siepmann F, Klose D. *Biomacromolecules.* 2005; 6:2312. [PubMed: 16004477]
22. Birnbaum DT, Brannon-Peppas L. *J Biomater Sci Polym Ed.* 2003; 14:87. [PubMed: 12635772]
23. Yoo HS, Lee KH, Oh JE, Park TG. *J Controlled Release.* 2000; 68:419.
24. Yoo HS, Oh JE, Lee KH, Park TG. *Pharm Res.* 1999; 16:1114. [PubMed: 10450940]

	PIXEL MODELS (2D)		VOXEL MODELS (3D)		
	n = 4	n = 8	n = 6	n = 18	n = 26
$d = \sqrt{1}$	4	4	6	6	6
$d = \sqrt{2}$	0	4	0	12	12
$d = \sqrt{3}$	0	0	0	0	8
$CCDF = \frac{\sum_{i=1}^3 d \times n(d = \sqrt{i})}{Z}, Z \begin{cases} 8 \vee 2D \\ 26 \vee 3D \end{cases}$	0.50	1.21	0.23	0.88	1.42
$SVR = \frac{1 + \sum_{i=1}^3 n(d = \sqrt{i})}{\frac{4}{3} \pi (1.5)^3}$	-	-	0.42	1.27	1.84
Pictorial Depiction					

**Fig. 1.**

Geometric implications of pixel and voxel neighborhoods. The distance ( $d$ ) between the center of a pixel (in 2D) or voxel (in 3D) and the center of its immediate neighbors is 1 or 2 or 3 units. The center to center distance factor (CCDF) and spherical volume ratio (SVR) are used to calculate the neighborhood ( $n$ ) that best approximates a circle (or a sphere) enclosed within the 2D pixel (or 3D voxel) grid. A schematic representation of the neighborhoods is depicted with the pixels/voxels colored black (center), red ( $d = 1$ ), blue ( $d = 2$ ) and green ( $d = 3$ ).

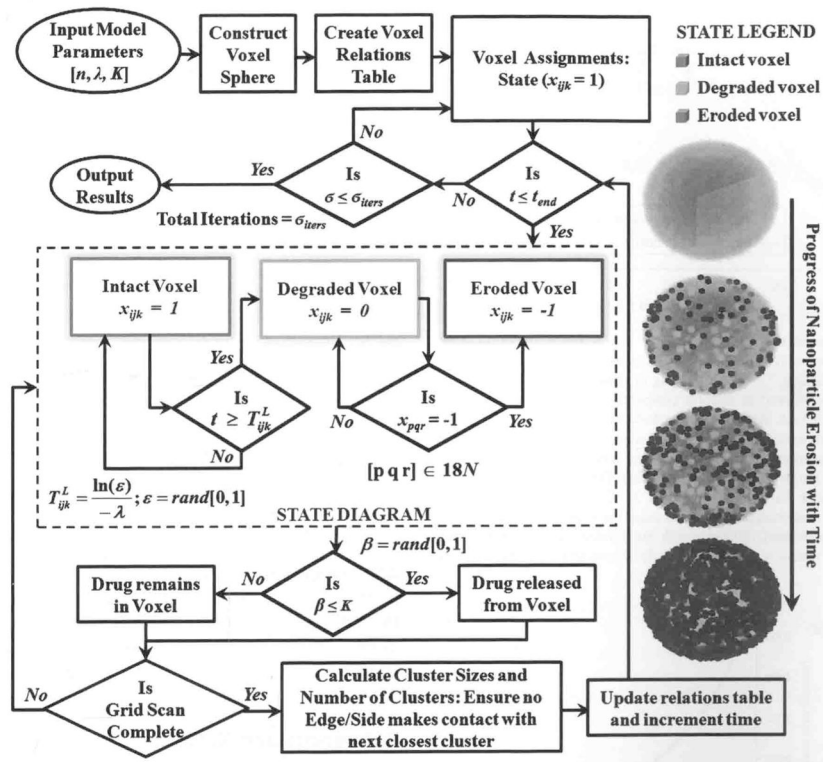
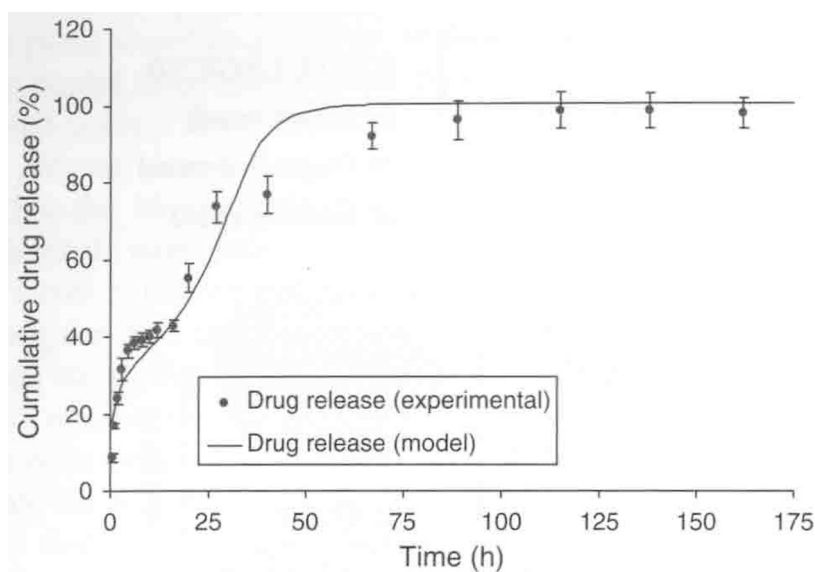


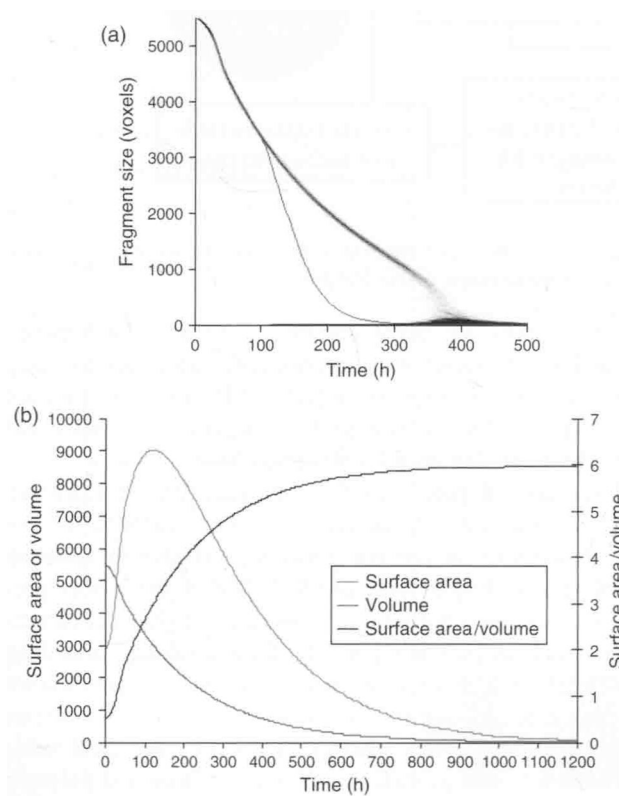
Fig. 2.

Flowchart and state diagram governing the voxel-based model. An illustration of the principles involved in estimation of voxel state transitions, nanoparticle fragmentation and drug release. A visualization of polymeric nanoparticle bulk erosion is also depicted.

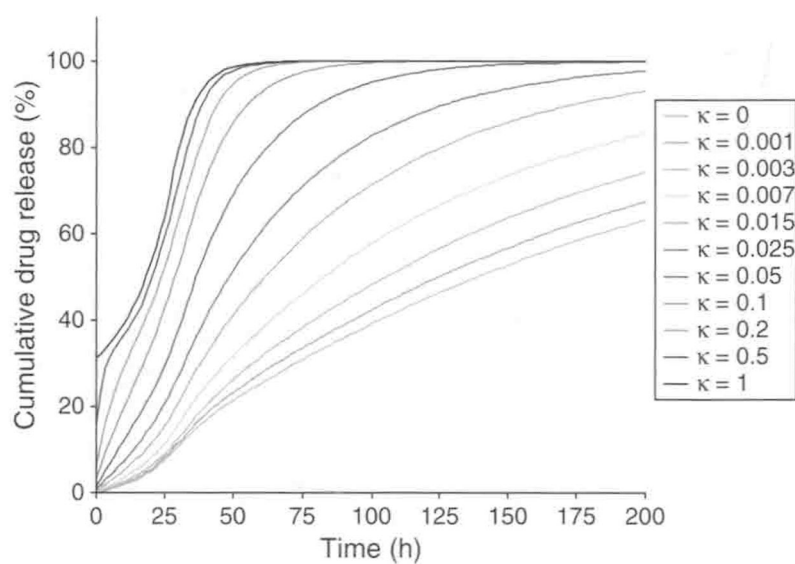
**Fig. 3.**

Dexamethasone release from PLGA nanoparticles *in vitro*. Nanoparticles were formulated using a modified emulsion-solvent evaporation technique.<sup>19,20</sup> Briefly, 25 mg of dexamethasone and 50 mg of PLGA were allowed to dissolve completely in 2.5 mL acetone before addition of 0.5 mL methanol and emulsification into an aqueous 2% PVA solution with sonication. Nanoparticles were separated from free drug by ultracentrifugation and were demonstrated to have a mean particle diameter of 115 nm by dynamic light scattering. Drug release was quantified by HPLC after dialysis against PBS at 37 °C with gentle shaking. Simulations of drug release were coded using the C programming language and were performed 100 times with mean values shown. Experimental results are means  $\pm$  s.e.m. ( $n = 3$ ). Parameters:  $N = 5497$  voxels,  $\kappa = 0.5$ .



**Fig. 4.**

Simulation of drug release and nanoparticle fragmentation. (a) Model representation of nanoparticle fragmentation: black scatter represents variability between different simulations, blue line represents average fragment size. (b) Simulation results for surface area (exposed voxel area) and volume (voxel count) during nanoparticle fragmentation.



**Fig. 5.**

Influence of the model parameter  $\kappa$  on drug release. Simulation results for  $\kappa$  values between 0 and 1 demonstrate the capacity of the model for simulating the release of drugs with distinct diffusion and dissolution characteristics. Model parameters:  $N = 5497$  voxels, iterations = 100.